

Applicant: Ilya Trakht
Serial No.: 09/767,578
Filed: January 23, 2001
Page 2

REMARKS

Claims 29-34 are pending in the subject application. No claim has been added, cancelled or amended herein.

In view of the arguments set forth below, applicant submits that the Examiner's rejections made in the April 23, 2004 Office Action have been overcome. Applicant therefore respectfully requests that the Examiner reconsider and withdraw these rejections.

The Claimed Invention

This invention provides a method for producing a monoclonal antibody from a tetroma cell formed by fusing a lymphoid cell capable of producing antibody with a trioma cell which does not produce any antibody, wherein the trioma cell is obtained by fusing a heteromyeloma cell which does not produce any antibody with a human lymphoid cell. The use of a heteromyeloma cell to generate the fusion partner trioma cell was neither known nor suggested in the prior art.

Rejections under 35 U.S.C. §103(a)

The Examiner rejected claims 29-33 under 35 U.S.C. §103(a) as allegedly unpatentable over Oestberg et al. (U.S. Patent No. 4,634,664) in view of Gustafsson et al. (Hum. Antibod. Hybridomas [1991] 2: 26-32). The Examiner stated that applicant's arguments have been considered and deemed not persuasive.

The Examiner stated that Oestberg et al. teach xenogeneic hybridoma fusion partners that do not produce antibody and the use of said cells as fusion partners to produce monoclonal antibodies upon fusion with an antibody-producing cell (citing

Applicant: Ilya Trakht
Serial No.: 09/767,578
Filed: January 23, 2001
Page 3

column 2, last paragraph and column 3). The Examiner also stated that Oestberg et al. teach that the antibody-nonproducing xenogeneic hybridoma fusion partner can be made by fusing a myeloma cell to a human lymphocyte (citing column 2, last paragraph, continued on column 3). The Examiner further stated that Oestberg et al. teach that the myeloma cell used can be a hybrid cell formed from the fusion of two cells (citing column 2, last paragraph). The Examiner concluded that Oestberg et al. thus teach use of a three-cell-containing xenogeneic hybridoma fusion partner that does not produce antibody and the use of said cells as fusion partners to produce monoclonal antibodies. The Examiner acknowledged that Oestberg et al. do not teach that their fusion partner cell is a trioma as per the definition of the term in the specification (e.g., "trioma" as a cell line formed from the fusion of three cells wherein a human-murine hybridoma is fused with a human lymphoid cell). The Examiner also noted that the human-murine hybridoma used in the trioma as defined in the specification could not produce antibody, allegedly because such a cell could not be used as a fusion partner.

The Examiner stated that Oestberg et al. teach heteromyeloma cell fusion partners (e.g., mouse myeloma/human fused cells, citing claim 14). The Examiner also stated that Gustafsson et al. disclose that the term heteromyeloma encompasses a mouse myeloma cell fused to a human PBL (citing the abstract). The Examiner asserted that said heteromyeloma would be the same as the antibody-nonproducing human-murine hybridoma used in the trioma as defined in the specification. The Examiner concluded that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced the claimed method because (1) Oestberg et al. teach the claimed method except for use of a trioma cell line formed from the fusion of three cells, wherein a human-murine

Applicant: Ilya Trakht
Serial No.: 09/767,578
Filed: January 23, 2001
Page 4

hybridoma is fused with a human lymphoid cell; (2) Oestberg et al. teach use of three-cell antibody-nonproducing xenogeneic hybridoma fusion partner containing a hybrid myeloma cell; and (3) Oestberg et al. and Gustafsson et al. both teach human heteromyeloma cells (mouse-human hybrid myeloma cell line).

The Examiner stated that one of ordinary skill in the art would have been motivated to produce the claimed method because Oestberg et al. teach use of hybrid myelomas as the fusion partner with an antibody-nonsecreting (*sic*) human lymphocyte (citing column 2, last paragraph, continued on next page) to form a three-cell antibody-nonsecreting fusion partner, and Oestberg et al. and Gustafsson et al. both teach heteromyeloma cell fusion partners (e.g., mouse-human fused cells). The Examiner also stated that the antibody-producing hybrid cells can be used *in vitro* or *in vivo* to produce antibody (citing claim 18). The Examiner further stated that the cells are grown *in vitro* under conditions in which antibody is produced (citing the Examples). The Examiner additionally stated that Oestberg et al. teach freeze storage of desired antibody secreting cells (citing column 7, penultimate paragraph).

In addition, the Examiner stated that the various assay steps recited in claim 30 involve steps known in the art for immunoassays (citing the Examples in Oestberg et al., and Gustafsson et al.). The Examiner also stated that the use of a negative control in immunoassays (e.g., a sample not containing the antigen as a background control) as a basis of comparison to a positive result is well known in the art (citing, for example, Gustafsson et al., page 28, column 1, Immunoglobulin-ELISA). The Examiner further stated the condition recited in claim 30 could be any of the diseases known in the art which are disclosed in column 4 of Oestberg et al.

Applicant: Ilya Trakht
Serial No.: 09/767,578
Filed: January 23, 2001
Page 5

In response, applicant respectfully traverses this rejection of claims 29-33.

As argued in his February 20, 2004 Communication, applicant maintains that the Examiner has failed to satisfy all three prongs of the requirements for establishing a *prima facie* case of obviousness. First, Oestberg et al., in combination with routine skill, does not provide any suggestion or motivation to make the subject invention using a heteromyeloma cell to form a "trioma" cell. Applicant note the important definition of the trioma cell as a cell formed from the fusion of a human-murine heteromyeloma cell which does not produce any antibody with a human lymphoid cell (see specification at page 9, lines 15-19). Second, it does not provide any expectation of success in making and using such a heteromyeloma cell or a trioma cell. Third, this reference does not teach the claimed elements of the use of a heteromyeloma cell and a trioma cell.

Applicant notes that the trioma cell recited in claims 29 and 30 is made, in relevant part, by first fusing a human myeloma cell with a mouse myeloma cell to form a heteromyeloma cell. This heteromyeloma cell is then fused with a human lymphoid cell to form a trioma fusion partner cell. By contrast, Oestberg et al. teach the use of a "xenogeneic hybridoma cell" (i.e., a heterohybridoma), which is not a heteromyeloma cell. Applicant notes that in his February 20, 2004 Communication (see pages 4-5), he identified specific passages in Oestberg et al. that confirm Oestberg et al.'s use of a heterohybridoma. Thus, this element of the subject claims, i.e., the use of a heteromyeloma cell to generate a fusion partner, is not taught in Oestberg et al.

In response to this factual distinction previously explained by applicant between Oestberg et al.'s heterohybridoma and the subject

Applicant: Ilya Trakht
Serial No.: 09/767,578
Filed: January 23, 2001
Page 6

invention's heteromyeloma, the Examiner repeats his semantic argument that "heterohybridoma" and "heteromyeloma" describe the same cell populations because the terms are allegedly used interchangeably in the subject specification. In this regard, the Examiner stated that the specification does not specifically define the terms heteromyeloma or heterohybridoma. The Examiner further stated that the specification, however, defines "trioma" as a cell line formed from the fusion of three cells wherein a human-murine hybridoma is fused with a human lymphoid cell (citing page 23, lines 19-24). The Examiner further stated that the specification also discloses that "[t]he present invention provides a trioma cell obtained by fusing a heteromyeloma cell which does not produce any antibody with a human lymphoid cell" (citing page 3, lines 15-17). The Examiner asserted that the only way these two statements can be reconciled is if the two terms (i.e., human-murine hybridoma [a.k.a. heterohybridoma] and heteromyeloma) are used interchangeably.

Applicant respectfully disagrees with the Examiner's position that the terms "heterohybridoma" and "heteromyeloma" are synonymous, and rejects the suggestion that the terms are used interchangeable in the specification. As previously explained in his September 29, 2003 Amendment and February 20, 2004 Communication, applicant maintains that "heterohybridoma" and "heteromyeloma" are not equivalent terms. Indeed, the subject specification explicitly distinguishes between the use of heterohybridomas, as described by Oestberg, and heteromyelomas as described in the subject specification, as fusion partners. Thus, the specification states at page 2, lines 29-34:

In order to improve growth characteristics and stability of humAb production, heterohybrids between mouse myeloma cells and human lymphocyte [i.e., heterohybridomas] (Oestberg L, and Pursch E., 1983) as well as heteromyelomas (Kozbor D, et. al., 1984) are used as the fusion partners. (emphasis

Applicant: Ilya Trakht
Serial No.: 09/767,578
Filed: January 23, 2001
Page 7

added)

This statement confirms unequivocally that the terms "heterohybridoma" and "heteromyeloma," as used in the subject specification, refer to distinct groups of cells. Further, it clearly demonstrates that the terms are not used interchangeably in the specification as the Examiner continues to allege.

In the present Office Action, the Examiner attempts to support his semantic argument by pointing to Gustafsson et al.'s disclosure (citing the abstract) that a heteromyeloma is formed by fusion of a mouse myeloma cell and a human PBL.

In response, applicant contends that, at most, Gustafsson et al. simply reveals a tendency for careless and inconsistent usage of the terminology regarding this art in the scientific literature. Applicant understands the fusion of a mouse myeloma cell and a human PBL to generate an antibody-producing heterohybridoma and not a heteromyeloma as stated by Gustafsson et al. Applicant notes that the same Gustafsson et al. reference cited by the Examiner states that heterohybridomas are "obtained by fusing human B cells with mouse myeloma cells" (see page 26, right col., first full paragraph), which is inconsistent with the sentence in the abstract cited by the Examiner concerning the formation of a heteromyeloma. In fact, a perusal of Gustafsson et al. suggests that they use the term "heteromyeloma" to describe the hybrid cell formed from a fusion of cells from different species in which at least one of the partners is a myeloma. Further, it appears that if such a hybrid cell secretes an antibody, then Gustafsson et al. may also describe it as a heterohybridoma.

Applicant notes that his usage of the relevant terms in the subject specification, differs from that of Gustafsson et al. Thus, applicant reserves the term "heteromyeloma" for the

Applicant: Ilya Trakht
Serial No.: 09/767,578
Filed: January 23, 2001
Page 8

product of a fusion of two different immortal cell lines, especially myeloma lines, from one or different species (e.g., mouse myeloma x human myeloma). Applicant defines a "hybridoma" as an antibody-producing hybrid cell formed from the fusion of a normal lymphocyte (e.g., a T or B cell) and an immortal lymphoid cell (e.g., a myeloma or lymphoblastoma) or an immortal hybrid cell (e.g., a heteromyeloma). Further, applicant defines a heterohybridoma as an antibody-producing hybrid cell formed from fusion of two different hybridomas, though the term is also used to describe an antibody-producing hybrid between a normal lymphocyte and an immortal cell line (e.g., a myeloma) from different species (e.g., human lymphocyte x mouse myeloma). Applicant notes that his definitions are consistent with those of Gillett (2001), attached hereto as **Exhibit A**, as posted on the University of Manchester's Computer Assisted Learning site (http://cal.man.ac.uk/student_projects/2001/mnqgb8mjg/Murine.html).

Notwithstanding the above definitions, applicant acknowledges that the relevant terms may commonly be incorrectly used by persons skilled in the art, for example, as transitional terms to show the origin of a cell line. Thus, an antibody-nonproducing variant cell line that is derived from a heterohybridoma may often be labeled a "heterohybridoma" to reveal its origin, although an antibody-nonproducing cell, by definition, cannot be a hybridoma or a heterohybridoma.

In view of this admittedly inconsistent usage of the relevant terminology in this art, applicant contends that the Examiner's emphasis on purely semantic differences between the terms "heteromyeloma" and "heterohybridoma" distracts from the substantive differences between Oestberg's method and applicant's claimed method. Applicant therefore restates the salient features of these two methods, which emphasizes their substantive differences, as follows.

Applicant: Ilya Trakht
Serial No.: 09/767,578
Filed: January 23, 2001
Page 9

The Oestberg et al. method that is closest to applicant's method involves the fusion of an immortal mouse cell line, e.g., the SP-2 mouse myeloma, with a nontumorous human cell line, e.g., a human PBL, to produce an inter-specific "xenogeneic hybridoma" (see col. 2, line 60 to col. 3, line 2; col. 4, line 59 to col. 5, line 4; col. 6, lines 4-8). Applicant notes that such a xenogeneic hybridoma is ordinarily not suitable for use as a fusion partner with an antibody-producing lymphocyte (unless the intention is to produce bi-specific antibodies) since it itself unstably secretes antibodies. However, it is possible to select for antibody-nonproducing variants of the xenogeneic hybridoma. Thus, Oestberg et al. describe isolating five clones which showed fast growth and no antibody production after five weeks of selection from a "large number of hybrids" (col. 5, lines 5-7; col. 6, lines 24-27). One of these five clones, designated SPAZ-4, was further characterized (col. 6, lines 29-34). SPAZ-4, a mutant antibody-nonsecreting heterohybridoma, is Oestberg et al.'s fusion partner line which can be fused with a human PBL to produce a hybridoma which secretes a specific human antibody (see col. 5, lines 15-45; cols. 6-7, Example 2).

In contrast to the method of Oestberg et al., applicant's method utilizes two antibody-nonsecreting myeloma cell lines, e.g., human RPMI 8226 and mouse P3.X63.Ag.8 653, as the starting materials. Fusion of these myeloma lines produces a stable heteromyeloma, e.g., B6B11 (see the specification at, *inter alia*, page 29, lines 7-14 and 30-33; page 35, lines 2-7). Because it is derived from antibody-nonsecreting myelomas, the heteromyeloma is necessarily an antibody-nonsecreting hybrid. Applicant emphasizes that, unlike Oestberg et al.'s xenogeneic hybridoma which unstably secretes antibodies, the instant heteromyeloma can be directly used as a fusion partner with a human, antibody-producing lymphocyte. Thus, applicant's method bypasses the production of an unstable antibody-secreting hybrid line from

Applicant: Ilya Trakht
Serial No.: 09/767,578
Filed: January 23, 2001
Page 10

which an antibody-nonsecreting variant has to be isolated.

Applicant reiterates that, stripped of the labels used to identify the cell lines, it is clear that the formation and use of an antibody-nonsecreting hybrid cell, formed from the fusion of two antibody-nonsecreting myelomas, is a new and nonobvious element of claims 29 and 30 which is not taught by Oestberg et al. Applicant respectfully submits that in the Examiner's focus on whether the terms "heteromyeloma" and "heterohybridoma" are used interchangeably in the specification, he overlooks a very significant innovation of the instant method over that of Oestberg et al. In addition, applicant notes that Oestberg et al. neither suggests this innovation nor provides any expectation that it would succeed.

Before discussing the second innovative feature of the subject invention, applicant recalls the Examiner's statement mid-way on page 2 of the Office Action that "the human-murine hybridoma used in the trioma as per defined in the specification could not produce antibody, because such a cell could not be used as a fusion partner." In response, applicant respectfully wishes to correct the Examiner's understanding of the properties of "the human-murine hybridoma used in the trioma."

First, applicant notes that his so-called "human-murine hybridoma" (actually a heteromyeloma) does not produce antibodies precisely because it is formed from the fusion of two antibody-nonsecreting myelomas which is one of the essential innovations of applicant's method. In addition, applicant notes that the nonsecretion of antibodies is an important requirement of a fusion partner cell which is to be fused with an antibody-producing lymphocyte. Indeed, this requirement explains the necessity for Oestberg et al. to select an antibody-nonsecreting

Applicant: Ilya Trakht
Serial No.: 09/767,578
Filed: January 23, 2001
Page 11

variant from their xenogeneic hybridomas to use as a fusion partner cell.

Second, contrary to the Examiner's assertion, applicant notes that his "human-murine hybridoma" can be used as a fusion partner. In this regard, applicant respectfully directs the Examiner's attention to the specification at, *inter alia*, page 29, lines 7-20, page 35, lines 21-29, and page 42, lines 27-29. These sections of the specification disclose that the heteromyeloma B6B11 fuses with human splenocytes and lymph node lymphocytes with a frequency comparable to murine hybridoma formation. Further, the resulting hybrids are readily cloned, grow in serum-free media, and stably secrete antibodies.

Applicant also recalls the Examiner's statement at the top of page 2 of the Office Action that Oestberg et al.'s myeloma cell used to make their xenogeneic hybridoma can be a hybrid cell formed from the fusion of two cells. In this regard, applicant notes that the SP-2 myeloma line used by Oestberg et al. was derived from a hybridoma, which itself was formed from fusion of the mouse P3-X63-Ag8 myeloma and mouse spleen cells (see Oestberg et al., col. 4, lines 59-65). Accordingly, whereas the Examiner acknowledges that Oestberg et al. do not teach that their xenogeneic hybridoma is a trioma as defined in the subject specification, the Examiner states that Oestberg et al. do teach use of a three-cell-containing xenogeneic hybridoma fusion partner that does not produce antibody and the use of said cells as fusion partners to produce monoclonal antibodies. The Examiner thus appears to be suggesting that Oestberg et al. in fact teach the use of a trioma fusion partner, even if that trioma fusion partner does not quite meet the definition of the term "trioma" in the specification.

Applicant: Ilya Trakht
Serial No.: 09/767,578
Filed: January 23, 2001
Page 12

In response, applicant notes that this line of argument of the Examiner actually highlights a second critical element of applicant's method which is missing from the method of Oestberg et al. Applicant notes that notwithstanding the fact that the SP-2 line was originally derived from two mouse cell lines, the genetic background of the SP-2 line is entirely a mouse background. Thus, when SP-2 is fused with human PBL to produce a "xenogeneic hybridoma," this hybrid line, though originally derived from three cell lines, has a human to mouse genetic background ratio of 1:1. Accordingly, when the xenogeneic hybridoma is fused with a human PBL to generate a hybridoma which secretes a specific antibody, this antibody-secreting hybridoma has a human to mouse genetic background ratio of 3:1.

By contrast, applicant's heteromyeloma, formed from the fusion of human myeloma and mouse myeloma lines, has a human to mouse genetic background ratio of 1:1. As noted above, this heteromyeloma can be fused with high efficiency to a human splenocyte or lymph node lymphocyte to generate an antibody-secreting hybridoma (see specification at page 29, lines 7-20, page 35, lines 21-29, and page 42, lines 27-29). However, the frequency of fusion of the heteromyeloma with PBL is much lower than fusion with splenocytes or lymph node lymphocytes (see page 42, lines 27-31 of the specification).

To overcome the problem of low fusion efficiency with PBL, the heteromyeloma was fused with human lymph node lymphocytes to produce antibody-nonsecreting "trioma" cells, designated "modified fusion partner" (MFP) cells (see page 42, line 33 to page 43, line 8 of the specification). Thus, this trioma cell, which in applicant's method is the ultimate fusion partner cell and derived from three fused cells (two human and one mouse), has a human to mouse genetic background ratio of 3:1. Applicant contrasts Oestberg et al.'s "xenogeneic hybridoma" which, though

Applicant: Ilya Trakht
Serial No.: 09/767,578
Filed: January 23, 2001
Page 13

originally derived from three cell lines, has a human to mouse genetic background ratio of 1:1.

Significantly, applicant's trioma fusion partner cell is capable of fusing efficiently with a human PBL to generate an antibody-secreting tetroma which has a human to mouse genetic background ratio of 7:1. Thus, the genetic background of applicant's antibody-secreting hybridoma has a human component which is more than twice as high as that in Oestberg et al.'s antibody-secreting hybridoma.

Applicant contends that the higher human genetic component of his trioma fusion partner cell compared to Oestberg et al.'s fusion partner cell confers important functional advantages. Applicant's own comparison of his fusion partner cell with Oestberg et al.'s fusion partner cell has revealed that, first, his trioma cell exhibits a higher frequency of fusion with human PBL. Second, fusion of applicant's trioma with human PBL results in tetromas that exhibit more stable antibody production. Applicant speculates that the higher frequency of fusion and greater stability of antibody production results from the higher human genetic component in his trioma fusion partner cell compared to Oestberg et al.'s fusion partner cell.

Applicant respectfully submits, therefore, that there is no merit in the Examiner's conclusion on pages 3-4 of the Office Action that applicant's method is obvious over Oestberg et al.'s method, in part 'because Oestberg et al. teach the claimed method except for use of a trioma cell line formed from the fusion of three cells, wherein a human-murine hybridoma is fused with a human lymphoid cell, [but that] Oestberg [et al.] teach use of a three-cell nonantibody-producing xenogeneic hybridoma fusion partner..." Applicant emphasizes that in the specification's definition of "trioma," not merely is the

Applicant: Ilya Trakht
Serial No.: 09/767,578
Filed: January 23, 2001
Page 14

trioma cell line derived from the fusion of three cells, but also a human-murine hybrid cell is fused with a human lymphoid cell. Thus, applicant maintains that the Examiner's focus on "trioma" as indicating a three-cell origin obscures functionally important differences between Oestberg et al.'s and applicant's methods.

In summary, therefore, applicant maintains that, as set forth above, the distinctions between (1) Oestberg et al.'s "xenogeneic hybridoma" (a heterohybridoma) and applicant's heteromyeloma, and (2) a "trioma" fusion partner cell as defined in the specification versus Oestberg et al.'s three-cell-derived fusion partner cell are not merely semantic but, instead, reveal important, functional differences between the two methods. Applicant reiterates that his method comprises nonobvious innovations which confer significant functional advantages over the method of Oestberg et al. in the production of human antibodies, and that these innovations comprise elements that are absent from Oestberg et al.'s method. Applicant maintains, therefore, that the Examiner fails to satisfy the third criterion, per M.P.E.P. §2142, for establishing a *prima facie* case of obviousness with respect to claims 29 and 30.

Regarding applicant's comments about the Exhibits from The Dictionary of Cell and Molecular Biology, the Examiner stated that these Exhibits define the terms "hybridoma" and "myeloma" but that these terms are not the terms under consideration. The Examiner stated that applicant then goes on to interpret what he thinks the terms might mean in the context of "heteromyeloma." The Examiner further stated that, however, the Gustafsson et al. reference specifically teaches that a heteromyeloma is formed by fusion of mouse myeloma cells and human PBLs (citing the abstract). The Examiner also stated that, furthermore, regarding applicant's comments about what the term

Applicant: Ilya Trakht
Serial No.: 09/767,578
Filed: January 23, 2001
Page 15

"heteromyeloma" means, there is no evidence of record to support applicant's assertions because applicant is disclosing his own interpretation of the meaning of said term based on the definition of "myeloma." The Examiner quoted M.P.E.P. §2145 (I) as follows:

The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness.").

In addition, regarding applicant's comments about specific examples disclosed in the specification, the Examiner stated that while said examples may disclose human myeloma/mouse myeloma hybrid cells, the term "heteromyeloma" is not disclosed in the specification as only encompassing such cells and that the prior art clearly indicates that "heteromyeloma" encompasses mouse myeloma/human PBL hybrid cells.

In response, applicant again directs the Examiner's attention to the published definitions of the terms "heterohybridoma" and "heteromyeloma", attached hereto as **Exhibit A**, which are consistent with applicant's usage of these terms in the specification. In addition, applicant maintains that whereas the term "heteromyeloma" is not disclosed in the specification as only encompassing hybrid cells formed from fusion of different myeloma lines, the specification also does not contain any statement indicating that these two terms are synonymous or interchangeable. On the contrary, as discussed in detail in applicant's previous Communication filed February 20, 2004, the subject specification clearly uses the terms "heterohybridoma" and "heteromyeloma" to refer to distinct groups of cells, and clearly demonstrates that the terms are not used

Applicant: Ilya Trakht
Serial No.: 09/767,578
Filed: January 23, 2001
Page 16

interchangeably.

Applicant respectfully submits that the above remarks obviate the rejection of claims 29 and 30 under 35 U.S.C. §103(a), and requests that the Examiner reconsider and withdraw the rejections.

Claims 31-33 depend, directly or indirectly, from claim 29. Applicant therefore submits that the arguments made in relation to claims 29 and 30 also obviate the rejections of claims 31-33. Accordingly, applicant also requests that the Examiner reconsider and withdraw the rejection of claims 31-33 under 35 U.S.C. §103(a).

Objection

The Examiner stated that claim 34 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form.

In response, applicant respectfully submits that based on the remarks made herein, the rejection of base claim 29 should be withdrawn, thereby rendering the instant objection moot.

Conclusion

In view of the remarks and arguments set forth above, applicant respectfully requests that the Examiner reconsider and withdraw the claim rejections set forth in the April 23, 2004 Office Action, and earnestly solicits allowance of all claims pending in the subject application.

If a telephone conference would be of assistance in advancing the prosecution of the subject application, applicant's undersigned


Applicant: Ilya Trakht
Serial No.: 09/767,578
Filed: January 23, 2001
Page 17

attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the enclosed fee of FOUR HUNDRED AND NINETY DOLLARS (490.00) for a three-month extension of time, is deemed necessary in connection with the filing of this Communication. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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